REMARKS

Claims 1 and 3-33 are pending. Claims 1, 3-5, 7, 10, 11, 13, 16-18, 20, 21, and 28 have been amended. No new matter is added by these amendments.

The Examiner has withdrawn most of the previous rejections of the claims under 35 U.S.C. 103(a) and 101. The remaining rejections, and the new rejections raised in this Final Office action, are addressed below.

Applicant thanks the Examiner for the courtesy of a telephonic interview on August 17, 2010 with Applicant's representatives David Johnson and Muriel Liberto. Examiners Kennedy and Kubelik participated in the call. The obviousness rejection was discussed as applied to proposed amended claims 1 and 20 and in view of the data presented in the Declaration filed with Applicant's March 18, 2010 response. With respect to claim 1, Examiner Kennedy stated that further data should be provided showing that formoterol fumarate is primarily in the dihydrate form at water contents between 4.4% and 4.8%. Specifically, the Examiner stated that further data showing the crystalline structure of formoterol fumarate having water content above 4.4%, such as 4.6% and 4.8%, would be desirable. Applicant submits with this response a further Declaration under 37 C.F.R. 1.132 by Dr. Rudi Mueller-Walz to address the Examiner's request for this data. With respect to claim to 20, no specific agreement was reached.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 3-19 and 21-33 are newly rejected as depending from a cancelled claim. The amendments to the claims render this rejection moot. Withdrawal of the rejection is requested.

Rejections under 35 U.S.C. § 103(a)

1. Claim 20: Davies in view of Clarke

Claim 20 remains rejected under 35 U.S.C. § 103(a) as unpatentable over Davies (US2005/0152846) in view of Clarke (US2002/0103260). Specifically, the Examiner cites Davies for describing a formulation comprising formoterol in which stability is improved by reducing the amount of water in the formulation to less than 500 ppm based on the total weight of the formulation. Office Action at p. 3, para. 2. In response to Applicant's argument that Davies fails to describe or suggest the desirable water content of a *suspension* formulation of formoterol fumarate dihydrate ("FF dihydrate"), the Examiner contends that Davies describes

suspension formulations of FF dihydrate,. Office action at p. 4, para. 3. In response, Applicant respectfully submits that the Examiner has misconstrued Davies. For the reasons set forth below, Applicant maintains that Davies does not describe or suggest a *suspension* formulation of FF dihydrate. Instead, the suspension formulations described by Davies are prior art formulations. And Davies therefore does not describe or suggest a *suspension* formulation comprising formoterol fumarate in which stability is improved by reducing the amount of water in the formulation.

The Examiner relies on paragraphs 10 and 39-41 of Davies. Office action at p. 4, para. 3. In paragraph 10, Davies describes the state of the prior art as including aerosol formulations in the form of both solutions and suspensions. This is clear from the context of the paragraph as well as its location in the Background section of the specification of Davies. In paragraph 39, Davies describes WO 98/34595 as referring to "aerosol formulations in the form of solutions or suspensions in which the propellant is a mixture of a HFA and carbon dioxide" in which the carbon dioxide acts as a stabilizer of the active compounds. This is clearly describing the formulations of WO 98/34595 and not Davies' invention. In paragraph 40, Davies describes WO 00/06121 as referring to "propellant mixtures for aerosol containing dinitrogen monoxide and a hydrofluoroalkane in the preparation of suspension and solution aerosols" in which dinitrogen monoxide acts as a stabilizer. Davies further notes that "[a]s far as LABAs such as formoterol fumarate and salmeterol xinafoate, *only examples referred to [sic] suspensions are reported.*" Emphasis added. Not only does this paragraph not describe the invention of Davies, it explicitly distinguishes the prior art as *only describing suspension formulations* of formoterol fumarate. This clearly supports Applicant's position that Davies does not contemplate suspension formulations of formoterol fumarate. Finally, in paragraph 41, Davies describes WO 99/65460 as referring to pressurized MDI's containing stable formulations of beta 2 receptor agonists (*i.e.*, formoterol fumarate) in suspension or solution. Again, this is not a description of Davies' invention but rather a description of a prior art formulation. Thus, none of the paragraphs relied upon by the Examiner to support the rejection describes Davies' invention.

In contrast, the specification of Davies' supports Applicant's position that Davies contemplates only *solution* formulations, and therefore that Davies can reasonably be relied upon only for describing a *solution* formulation of formoterol fumarate in which stability is improved by reducing the amount of water. *See e.g.*, para. 27 (describing the invention as providing a pharmaceutical aerosol *solution* formulation); para. 30 (describing a preferred embodiment as comprising formoterol fumarate in *solution*; para. 56 (describing the formulations of the invention as ones in which the active is *fully dissolved*), and the examples

beginning at para. 90 (each of which describes an aerosol *solution* formulation). Applicant previously noted that a reference describing conditions for stabilizing a *solution* formulation would not have suggested to the skilled person the same conditions for stabilizing a *suspension* formulation, because of the different factors affecting the stability of solution versus suspension formulations. In solution formulations, the *chemical* stability of the active *in solution* is the main factor. However, in suspension formulations, the active is not dissolved in the carrier but instead exists as a particle. Thus, it is the *physical* stability of the particles, mainly their tendency to agglomerate, that is the main factor. Different factors influence chemical stability in solution compared to physical stability as a particle in suspension. The finding that a particular factor, such as water content, influences stability of the active in solution, does not necessarily indicate that the same factor is important for physical stability of the particle in suspension. Accordingly, Applicant maintains that the description in Davies of *solution* formulations of formoterol fumarate which are stabilized by reducing the total water content of the formulation does not provide a reasonable expectation of success for stabilizing a suspension formulation of FF dihydrate by controlling its water content as specified by claim 20.

The Examiner contends that Davies provides a reason to lower the water content of a *suspension* formulation of FF dihydrate because, in the Examiner's view, the general teachings of Davies are that aerosol formulations, known to be in solution or suspension, have improved stability when water content is decreased. Office action at p. 4, para. 3 to p. 5, first para. However, this is not the general teaching of Davies. Davies teaches only that formoterol in *solution* in an HFA propellant and a cosolvent is extremely sensitive to residual humidity and that for water contents higher than 1500 ppm the amount of formoterol decreases to an extent that renders the formulation unacceptable for pharmaceutical purposes. Davies at paras. 34 and 35. Due to the different considerations in formulating solution versus suspension formulations discussed above, the skilled person would not, as the Examiner has done, generalize the teachings of Davies regarding solution formulations of formoterol to suspension formulations of formoterol.

In summary, while a reference may be relied upon for all that it would reasonably have suggested, including nonpreferred embodiments, it is not reasonable to rely upon a reference for that which it does *not* describe. And Davies does not describe or suggest an embodiment in which an aerosol *suspension* formulation of FF dihydrate is stabilized by reducing its water content.

The Examiner stated that Clarke was "merely cited to show a commonly used form of formoterol fumarate, the di-hydrate form." Office action at p. 5, para. 1. Accordingly, the

combination of Davies and Clarke fails to describe a suspension formulation of FF dihydrate having a moisture content of from 50 ppm to 800 ppm; nor does the combination provide any reason to make a suspension formulation of FF dihydrate having that specific water content, as required by claim 20. Accordingly, Applicant requests reconsideration and withdrawal of the rejection.

2. Clarke and the Trofast References

Claims 1, 7, 10, 13-16, 21, 23-24, 27, 28 and 32 are newly rejected under 35 U.S.C. § 103(a) as unpatentable over the same references as relied upon previously by the Examiner, US20020103260 ("Clarke"), in view of WO 92/18110 ("Trofast I") and WO 01/89491 ("Trofast II"). The rejection is traversed as applied to amended claim 1.

As a preliminary matter, and without conceding the correctness of the Examiner's remarks, but in an effort to further the prosecution of the subject application, Applicant notes that claim 1 has been amended to omit the term "about" and the term "comprising" has been replaced with "consisting essentially of" to emphasize that the claimed formulations consist primarily of the dihydrate form of formoterol fumarate which is the predominant form at the water contents specified in the claim. This is evidenced by the first Declaration under 37 C.F.R. 1.132 by Dr. Rudi Mueller-Walz submitted with Applicant's previous response and further by the second Declaration submitted with the present response. The data discussed in the declarations shows that the predominant crystalline form of formoterol fumarate at water contents within the claimed range is the dihydrate form.

In response to the Examiner's rejection of claim 1, and its dependent claims, over the combination of Clarke, Trofast I, and Trofast II, Applicant maintains that, even if the skilled person were to take from the combination of references the idea to dry formoterol fumarate prior to mixing it with other ingredients, the skilled person would not arrive at the claimed invention. This was demonstrated by the first Declaration of Dr. Rudi Mueller-Walz (made of record in previous response) which discussed the data showing that at water contents below the claimed range formoterol fumarate exists as an unstable mixture of the anhydrate and dihydrate forms. It is undisputed by the Examiner that there is no teaching or suggestion in the combination of references that would lead the skilled person to dry and then rehydrate the formoterol fumarate under controlled conditions until it reached a water content within the claimed range. Accordingly, the combination of references, even when combined as suggested by the Examiner, fails to lead predictably to the claimed invention. For this reason alone the rejection should be withdrawn.

Applicant also maintains that the combination of references does not in fact teach that a formulation containing FF dihydrate should be dried prior to mixing it with other ingredients, as contended by the Examiner. The Examiner contends that the Trofast references provide the motivation to make a suspension formulation of FF dihydrate having a reduced water content. Office action at p. 10, last paragraph. In support of this position, the Examiner characterizes the Trofast references as teaching that FF dihydrate *in the presence of lactose* should be dried to stabilize the FF dihydrate and that therefore *the references implicitly teach that water content influences stability*. Office action at p. 10, last para. to p. 11, first para. In response, Applicant submits that at most, Trofast II teaches that the *excipient* (lactose) should be dried before combining it with FF dihydrate. Regarding a powder mixture of FF dihydrate and lactose monohydrate, Trofast II states that "[b]y sorption of water a saturated *aqueous lactose solution* is formed at the surface of the powder mixture" and that "a certain amount of formoterol fumarate dissolves in this aqueous solution and is thereby susceptible to degradation." Trofast II at p. 2, lines 16-18 (emphasis added). Trofast II goes on to state that, "[t]herefore, the relative humidity, as well as storage temperature, will influence the stability *of the powder mixture*." *Id.* at p. 2, lines 19-20 (emphasis added). The Examiner continues to rely on this description in Trofast for suggesting to the skilled person that humidity affects the stability of FF dihydrate and that it should therefore be dried prior to mixing with other ingredients, such as lactose. In doing so, the Examiner ignores the explicit teachings of Trofast II that it is the excipient *lactose* that absorbs water (from the air) and should therefore be dried (or "conditioned"), prior to mixing with the FF dihydrate. This is further evidenced by the specific examples of Trofast II which show that it is the conditioned *lactose monohydrate* (and not FF dihydrate) that leads to the more stable powder mixture. Trofast II, Examples 1 and 2 at pgs 6-7 and Figure 1; see also general description of the process at p. 2 of Trofast II.

Finally, Applicant maintains for the reasons of record that whatever the Trofast references may describe to the skilled person about the stability of *powder* formulations containing FF dihydrate, they do not describe stable formulations of *suspension* formulations, much less a suspension formulation in which the FF dihydrate has a water content of 4.8 to 4.28% as required by claim 1. *See e.g.*, Applicant's response filed March 18, 2010 at p. 8, para. 3.

In view of the above, Applicant maintains that a *prima facie* case of obviousness has not been established with respect to claim 1, or its dependent claims. Accordingly, reconsideration and withdrawal of the rejection is requested.

3. Clarke and the Trofast References in View of Kordikowski

Claims 3-6, 21, 22, 26, and 33 remain rejected under 35 U.S.C. § 103(a) as unpatentable over Clarke in view of Trofast I and Trofast II and further in view of (US 2003/0223939 ("Kordikowski"). The rejection is traversed as it applies to amended claim 1 and its dependent claims.

With respect to amended claim 1, the Examiner cites Kordikowski for its description of formulations providing a Delivered dose having a variance of no more than 15% of the mean Delivered dose when stored at 40C and 75% humidity for up to 6 months. Office action at p. 11, last paragraph to p. 12, first paragraph. Kordikowski does not describe or suggest a formulation of formoterol fumarate di-hydrate in which the formoterol fumarate di-hydrate has a water content of 4.8 to 4.28% as required by claim 1. Accordingly, Kordiskowski does not remedy the deficiencies of Clarke, Trofast I, and Trofast II, as discussed above and Applicant requests reconsideration and withdrawal of the rejection.

3. Clarke and the Trofast References in View of Keller

Claims 8, 9, 11, 12, 18, 19, 25, and 29-31 remain rejected under 35 U.S.C. § 103(a) as unpatentable over Clarke in view of Trofast I and Trofast II and further in view of Keller (U.S. 6,475,467). The Examiner cites Keller for its teachings relating to the subject matter of dependent claims 8, 9, 11, 12, 18, 19, 25, and 29-31. Office Action at p. 13-16. The teachings of Keller do not remedy the deficiencies of Clarke, Trofast I, and Trofast II, as discussed above. Accordingly, Applicant request reconsideration and withdrawal of the rejection.

Double Patenting Rejection

The Examiner also maintained the provisional rejection of claim 20 over claim 20 of copending application no. 10/574,334 ("the '334 application") under 35 U.S.C. § 101 as directed to the same invention as the claim of the '334 application.

In response, Applicant will address this rejection at such time as one or more of the conflicting claims is otherwise in condition for allowance.

Applicant submits that the application is in condition for allowance and request an action for same. No additional fees, other than the fees authorized in connection with the filing of this paper, are believed due. However, if any additional fees are due, please charge the amount of any such fees, or credit any overpayment, to Deposit Account No. 50-0311, Attorney Reference No. **28069-623N01US**.

Respectfully submitted,

/Muriel Liberto/

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